REMARKS

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected Claims 1-4, 6-8, and 11-15 under 35 USC 112, first paragraph, as allegedly failing to comply with the requirement for written description. The Examiner stated that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner stated that genera "pharmaceutical compound" and "functional polymer" recited in the claims have not been sufficiently described to demonstrate possession thereof.

The Examiner stated that the example of ziprasidone in the specification is not sufficient to show possession of all pharmaceutical compounds. The Examiner stated that the genus of "pharmaceutical compounds" comprises materials having disparate functions and properties, for example hydrophilic or hydrophobic, anionic, cationic, zwitterionic, or neutral; and which may have one or more of a multitude of biological functions. According to the Examiner, the example of ziprasidone is not sufficient to show possession of all such materials in the context of the invention.

Applicants respectfully traverse. Note that the invention as recited in Claim 1 is directed to "a solid ionic conjugate". The claimed conjugate comprises the pharmaceutical compound and a functional polymer. The application describes that said ionic conjugate involves sufficient proton transfer between basic aspects or moieties of the pharmaceutical compound (or functional polymer as the case may be) and acidic aspects or moieties of the functional polymer (or pharmaceutical compound as the case may be). (See page 5, lines 20-26.)

Applicants submit that in assessing the written description requirement, the Examiner has focused on the number of examples provided in the application rather than the real inquiry, which is whether Applicants have adequately described their invention in the specification to convey to the public the subject matter which is being claimed (See MPEP, Section 2163, page 2100-165). Note that "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met . . . even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of invention that involves a biological macromolecule must contain a recitation of knows structure." *Falkner v. Inglis,* 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). Applicants submit that the aforementioned principle equally applies in the instant situation. The specification describes "pharmaceutical compound" in a way sufficient to convey to the public what Applicants are claiming. As discussed above, the specification is clear in indicating that the pharmaceutical compound is involved in an ionic conjugation with the functional polymer. It is true that

there are multitudes of pharmaceutical compounds, but their chemical structures are well known in the art. Those of ordinary skill in the art are well familiar with, once knowing the molecular structure of any pharmaceutical compound, being able to identify whether it is capable of ionic conjugation. "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. V. Monoclonal Antibodies*, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986). Additionally, as discussed, the subject specification provides description of those qualities which would render a pharmaceutical compound of being capable of ionic conjugation. For example, the specification indicates that basic, e.g. amine groups, or acidic, e.g. carboxyl groups, can provide suitable ionic attraction to generate ionic bonding whereby the conjugates of the invention form (see page 3, lines 20-24). Hence, Applicants maintain that the subject application provides adequate written description of the genus "pharmaceutical compounds" for purposes of its relevance to the claimed invention.

As for the "functional polymer", the Examiner stated that the examples are not commensurate in scope with the genus which includes a large variety of polymers with a diverse set of physical and chemical properties. In this regard, the Examiner stated that functionalized polymers may be bioabsorbable or non-bioabsorbable, erodable or non-erodable, natural or synthetic, hydrophilic or hydrophobic, neutral or cationic or anionic, and that they may contain one or more of a wide variety of functionalities including carboxylate, thiol, sulphonate, phosphate, alcohol, ketone, aldehyde, ester, ether, amine, and ammonium.

Applicants respectfully traverse, using the same principles recognized above. For purposes of the claimed invention, which is "a solid ionic conjugate", the relevant quality of a polymer within the genus "functional polymer" is the capability of ionic conjugation with the pharmaceutical compound, and this definition is provided in the specification. As with "pharmaceutical compounds", it is well known in the art which polymers would be capable of forming ionic bonds. Furthermore, the specification also provides description of "functional polymer" sufficient to convey to the public what the term used in the claims encompasses. For example, the specification states that, without limitation, such polymers include "carboxyl-bearing polyesters, copolyesters, polyalkylene carbonates and copolyester-carbonates; and amine-bearing polyesters, copolyesters, polyalkylene carbonates and copolyester-carbonates" (see page 3, lines 26-29). Other examples of functional polymers are also provided in the specification. Based on these remarks, Applicants kindly request that the Examiner reconsider and withdraw the rejection of Claims 1-4, 6-8, and 11-15 under 35 USC 112, first paragraph.

Rejection under 35 U.S.C. §102(a) or §102(e)

The Examiner rejected Claims 1, 2, and 4-7 as anticipated by Kim et al. (US 6,232,304) under 35 USC 102(a) or 102(e). The Examiner stated that Kim et al. discloses an ionic conjugate of ziprasidone and a cyclodextrin. According to the Examiner, cyclodextrin reads on "functional polymer". The Examiner stated that the first entry of Table 1 of Kim et al. (see Column 9 of Kim et al.) shows that the

free base form of ziprasidone is poorly soluble in water, but that its solubility is increases upon forming a combination with HPBCD or SBECD, both types of cyclodextrins.

Applicants respectfully traverse this rejection of Claims 1, 2, and 4-7. It is true that Kim et al. describe the combination of ziprasidone, which is a "pharmaceutical compound", and a cyclodextrin. But in order to anticipate a claim, a prior art reference must disclose each and every element of the claimed invention. Note that the claims of the subject application contain a "functional polymer" as an element. Kim et al. does not disclose a polymer. Contrary to the Examiner's assertion, a cyclodextrin is not a polymer. In this regard, Applicants submit in the Information Disclosure Statement herewith pages 165-168 of the Handbook of Pharmaceutical Excipients, Third Edition, edited by Arthur H. Kibbe (hereinafter "Kibbe"). Kibbe teaches that cyclodextrins are "crystalline, nonhygroscopic, cyclic oligosaccharides derived from starch" (see the second column of Page 165). Moreover, looking at the structure provided in Column 1 of Page 165 to show examples of cyclodextrins, one can see that none of the examples of cyclodextrins are ionic. Furthermore, the cyclodextrins depicted in Column 1 comprise only seven units and have molecular weights ranging from 972 to 1297. Thus, a cyclodextrin is not polymeric. It may be considered oligomeric, but not polymeric. Thus Kim et al. does not disclose the "functional polymer" element of each of the claims of the subject application.

Furthermore, Kim et al. also does not disclose any specific ionic conjugate, but "ionic" is another element of the invention as recited in the claims of the subject application. As explained in the preceding paragraph, Kibbe shows that cyclodextrins are not necessarily ionic in nature. Kibbe teaches that for cyclodextrins "the internal surface of the cavity is hydrophobic while the outside of the torus is hydrophilic" and that "this arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity so forming an inclusion complex" (Column 2, Page 165, of Kibbe). Thus, the interaction between guest molecule and cyclodextrin is not indicated by Kibbe to be ionic, but rather hydrophobic. Referring to the examples of cyclodextrin-ziprasidone combinations provided in Table I (Column 9) of Kim et al. (to which the Examiner also referred), note that the combination of ziprasidone free base and HPBCD does not involve an ionic conjugation. Neither ziprasidone free base nor HPBCD are ionic molecules. Nonetheless, the combination of ziprasidone free base and HPBCD resulted in the increase in aqueous solubility from 0.3 μA/ml to 0.26 mgA/ml. True, a combination of ziprasidone and a cyclodextrin can increase the solubility of ziprasidone, and this is taught by Kim et al. But the means taught by Kim et al. for achieving increased solubility are not the same as the means described in the subject application.

For the reasons explained above, Applicants contend that Kim et al. does not anticipate the instant Claims 1, 2, and 4-7 under 35 USC 102. Applicants respectfully request that the Examiner withdraw this rejection.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected Claims 3, 8, and 11-14 under 35 USC 103(a) as allegedly obvious over Kim et al. in view of Shalaby et al. (US 5,916,883). In this rejection, the Examiner relied on the teachings of Kim et al. discussed above and relied on Shalaby et al. for, inter alia, teaching the polymers of the instant Claims 3 and 8. More specifically, the Examiner stated that Shalaby teaches cyclodextrin derivatives having polymers such as polylactide, polyglycolide and polycapralactone grafted onto them. The Examiner stated that such polymers are suggested by Shalaby et al. for use in forming an ionic conjugate with drugs having ionizable amines (referring to Column 1, line 60, through Column 3, line 23, of Shalaby et al.) The Examiner stated that Shalaby et al. teaches that using such a cyclodextrin derivative is advantageous for effecting controlled release of the drug (referring to Example 5 and Table V of Shalaby et al.). According to the Examiner, it would have been obvious for a person of ordinary skill in the art at the time of the invention to use the cyclodextrin derivatives taught by Shalaby et al. in the invention described in Kim et al. The Examiner stated that Shalaby et al. teaches that controlled release can be effected by using the derivatised cyclodextrins and that this would provide motivation to apply Shalaby et al. to the teachings of Kim et al.

Applicants respectfully traverse this rejection. Applicants contend that Claims 3, 8 and 11-14 are not obvious over Kim et al. in view of Shalaby et al. The invention recited in the claims of the subject application is directed to a solid ionic conjugate comprising a pharmaceutical compound, wherein the conjugate has an aqueous solubility greater than that of the pharmaceutical compound.

It is true that Kim et al. describes a combination of a drug, namely ziprasidone, in combination with cyclodextrins. As discussed above, Kim et al. relates to a method for increasing the solubility of ziprasidone using the cyclodextrins. Kim et al. teaches that "the solubility of the compounds [which include ziprasidone] . . . form stable inclusion complexes with cyclodextrins" and that "such inclusion complexes are highly water soluble relative to the non-complexed drug" (Column 2, lines 17-22).

Shalaby et al. relates to combining polypeptide drugs with acylated cyclodextrins, which may be grafted to polyesters, to form polypeptide-cyclodextrin conjugates. But the resulting conjugates exemplified in Shalaby et al. have *lower* solubility than the unconjugated polypeptide. Note especially that Example 3 of Shalaby et al. refers to combining a cold *solution* of acetate salts of the unconjugated drug (a polypeptide selected from Kinerton, Lanreotide, and Decapeptyl) (emphasis added). Thus, the drug taught by Shalaby et al. was in a solution before being formed into a conjugate. However, after being conjugated with acylated β-cyclodextrin, as described in Example 3, the drug is "precipitated" and "the resulting precipitate was filtered, rinsed thoroughly with water, and air dried" (see Column 4, lines 31-40, of Shalaby et al.) Thus, the conjugate produced in Example 3 of Shalaby et al. appears to be *insoluble* in water. A person ordinarily skilled in the art would actually be directed away from combining Kim et al. and Shalaby et al. because applying the acylated cyclodextrin derivatives described in Shalaby et al. with ziprasidone described in Kim et al. would only be expected to decrease, rather than to

increase, the solubility of ziprasidone and further exacerbate ziprasidone's solubility problem which Kim et al. seeks to solve.

Conclusion

Based on the above remarks, Applicants submit that the claimed invention is patentable over the references cited by the Examiner and provided with the Information Disclosure Statement herewith. Applicants earnestly solicit the earliest possible notification of allowable subject matter.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, the Examiner is kindly invited to telephone Applicants' undersigned attorney at the number provided.

Respectfully submitted,

Date: May 25, 2007

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